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Castor Seed Poisoning in Humans: A Review

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Division of Cutaneous Hazards

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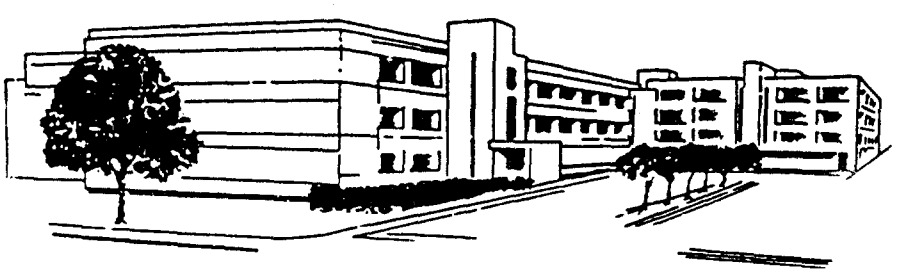

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This work reviews 314 cases of poisoning, including 15 deaths which occurred in humans as a result of castor seed ingestion between 1738 and 1988. Castor seed toxicity is due to ricin, a powerful phytotoxin present in the plant and concentrated in the seeds. Ingestion of castor seeds is extremely dangerous. In some parts of the world it is customary to eat one seed for purgative purposes. However, if they are well chewed, 2 or 3 seeds may be fatal to a child and 8 seeds to an adult. There is a latent period of 3 to 20 hours before the signs of toxicity appear. Manifestations of toxicity include internal hemorrhage and gastrointestinal irritation, nausea, violent vomiting, abdominal pain, severe diarrhea, dilatation of the pupils, and shivering. Convulsions occur in severe poisoning. The clinical features of poisoning give no clue to the diagnosis. The mode of action of ricin is not well understood, and at the present time no antidote for castor seed poisoning is available. Hospital treatment for the poisoned patient is entirely supportive. Following seed ingestion gastric lavage is employed to remove any remaining seeds from the stomach, followed by an appropriate dose of activated charcoal to bind the released ricin. Fluid and electrolyte balance must be maintained. In most cases the patient remains hospitalized for 3 to 14 days.

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PREFACE

In the evolutionary battle for survival, numerous organisms have developed a wide variety of defensive systems against potential aggressors. Prominent among such biological defenses are potent toxins, such as a toxic protein ricin, produced by the ubiquitous castor bean plant. Ricin is considered the most toxic substance of plant origin. A single gram of ricin would be lethal to 1.5 million guinea pigs, and 1 kg is lethal to 3.6 million people. Only tetanus, botulinum and diphtheria "supertoxins" are more powerful. Consumption of castor seeds has produced severe poisoning and death in many regions of the world; numerous cases have been recorded in the medical literature.

This review is a collection and summary of reports of castor seed poisoning by ingestion and ricin poisoning by injection from various parts of the world. The review clearly shows that more research effort is needed to develop an effective treatment against ricin poisoning. It would benefit both the civilian and the military communities, since the use of castor seed toxin against US citizens by subnational and terrorist groups cannot be excluded. The covert and clandestine use of castor seed poison recorded in the literature underlines an urgent need for an effective antidote. In addition, the antidote should be readily available to US troops undergoing survival exercises in various tropical and subtropical regions of the world where castor seeds can be easily mistaken for edible nuts.

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"All things are poison
and nothing is without poison.
The dose alone decides...."

Paracelsus, 1493-1541

INTRODUCTION

Some plants, bacteria, and animals contain proteins which may be highly toxic to other living organisms. The lethal dose of these toxins is minute, often a few micrograms per kg body weight. A particular toxin may affect specific organs or cells, and may immobilize or kill the intended victim within seconds. The mode of action of such toxins at the molecular level is not fully understood, but some toxins may inhibit the synthesis of specific tissue proteins, while others may be potent neurotoxins. Since early times such "superpoisons" have been a convenient tool to eliminate an adversary. They can be mixed easily with food, only minute amounts are needed, and they act quickly. Indeed, this form of killing became a lucrative business in ancient Rome, and it appears to have been resurrected in our times.

In 1978, ricin, a toxin present in castor beans, was used by an Eastern European Block agent operating in London to eliminate Georgi Markov, a journalist and an enemy of the Bulgarian regime. At about 13:30 on Thursday, September 7, a pellet containing the poison was implanted when an umbrella tip was jabbed into the back of Markov's right thigh. The pellet contained two channels, about 0.3 mm in diameter, drilled at right angles to each other, and containing about 500 ug of ricin. About 5h later Markov complained of feeling weak. The next day his temperature was elevated and he vomited. In the afternoon he had difficulty speaking. He was admitted to the hospital where it was noted that he looked hot and ill; his pulse was fast but regular,

and his blood pressure was normal. Some tender, swollen lymph glands were noted in his right groin. Markov's white cell count was 10,600. On Saturday afternoon his blood pressure dropped, his pulse rose to 160/min and his temperature fell. He was cold, sweating and dizzy. He was administered plasma expanders. His white cell count rose to 26,300. On Sunday he stopped passing urine and it was assumed that renal tubular necrosis had set in. Vomiting became more severe, with blood in the vomit. The electrocardiogram showed a complete block in the conductive system of the heart with evidence of ectopic beats in the ventricles. His white cell count rose to 33,200. The patient became confused, pulled out his intravenous lines and died shortly thereafter. At autopsy a pellet was found in the subcutaneous tissue beneath the superficial thigh wound. The autopsy revealed edema of the lungs, fatty change of the liver, hemorrhagic necrosis of the small intestines and hemorrhagic disruption of the lymph glands in the groin. Interstitial hemorrhages were also present in the intestines, testicles, pancreas, inguinal lymph glands and the adrenals. Subsequent histology showed small hemorrhages throughout the heart muscle, especially the conductive system (1).

Investigators administered ricin to a pig to compare the course of intoxication with that seen in Markov. About 6h after poisoning, the pig became sick, and its temperature and white cell count increased. The pig stopped eating but did not vomit. An electrocardiogram showed an extremely abnormal rhythm; the pig became subdued and died in a little over 24h. The heart had widespread small myocardial hemorrhages, and there was necrosis in the whole gut as well as the duodenum. All lymph nodes were hemorrhagic. The liver and kidneys appeared normal (1).

A pellet identical to the one removed from Markov's thigh was removed from the back of another man in Paris. This individual was in the hospital for 12 days with a fever from which he recovered (1).

At present no specific treatment for ricin poisoning exists; it is largely empirical. As ricin is difficult to detect in the body, it may have been used

for criminal purposes more often than we realize. Ricin is extremely toxic because it kills all cells. On a weight basis, ricin is twice as poisonous as cobra venom. It is a relatively small protein (M.W. about 65,000 daltons), consisting of two peptide chains: an active A-chain and a B-chain linked by a single disulfide bond. The B-chain is a lectin readily binding to galactose residues of glycoproteins and glycolipids located on the cell surface. The A-chain inhibits protein synthesis by inactivating the 60 S ribosomal subunit, which is then unable to bind to elongation factor 2. Ricin has been studied as a potential agent for treating malignancies. The toxin is successfully used against animal tumors, including Ehrlich ascites tumor cells and leukemias. A modified molecule of ricin attached to a specific antibody destroys a specific tumor or cancerous cell. Such immunotoxins are used as cancer chemotherapeutic agents (2,3).

The seeds of castor bean plant (Ricinus communis, L.) contain the largest amount of ricin, but all parts of the plant are probably toxic. Seeds are variable, smooth, flattened oval, 1/4 to 3/4 inch long, glossy dark or mottled brown, and are reported to have a pleasant taste. The plant has been cultivated since ancient times, and is often grown for ornamental purposes. It is a large plant, grown commercially for pharmaceutical and industrial use of its oil, and for landscaping because of its large, 12-lobed fan-like dark leaves. The plant is probably native to Africa. It easily adapts to various climates and grows in most tropical and subtropical lands. In the tropics the plant is a perennial, reaching a height of 30 to 40 feet. In the temperate zone it becomes an annual, attaining a height of 8 to 12 feet in a single season. In the United States it is common in the Carolinas, Florida, throughout the Gulf States and California. During WW I, the cultivation of the plant was temporarily stimulated by a demand for the oil as a lubricant, and considerable acreage was planted in Florida and California. Leading producers are China, India and Brazil. Castor bean plants are also grown in Russia, Costa Rica, Ecuador, Pakistan, Thailand, the Philippine Islands, Paraguay, Romania, Ethiopia, Sudan, Tanzania and Mexico. The current worldwide

annual production of castor seed is approximately 1,000,000 metric tons. In modern times castor oil has become an essential ingredient in the production of Nylon 11 (plastic and filament), sebacic acid (Nylon 6-10, plasticizers and jet engine lubricants), heavy-duty automotive and truck greases, coatings, inks, surfactants, polyurethanes and numerous oleochemical derivatives. The Castrol Oil Corporation is well known in this respect (4).

Numerous cases of violent illness resulting from eating castor beans have been reported in children and adults. In the tropics, it is a custom among some of the people to eat a single bean for its purgative effect, although modern medicine recognizes this practice as highly dangerous. In some countries holes are drilled through the seeds and they are strung together with or without other colorful seeds to form necklaces. Intentional ingestion of castor seeds, or rubbing the mucosa of the oral cavity with shelled seed was practiced, with some success, by the Italian troops in WW I to induce severe diarrhea and eye inflammation, in order to avoid military duty or result in discharge from the Army (5).

This report summarizes and critically reviews the available literature on castor bean poisoning in humans. It is hoped that this review will stimulate much needed research directed toward a better understanding of castor bean poisoning, accidental or intentional, and toward the development of rational medical therapy for this toxic material. There is another benefit to be accrued from such endeavors. In the tropics ground castor seeds are fermented and dried, and then sold for human food. Castor bean meal which remains after the oil has been removed contains about 40% protein. Detoxified castor bean meal, with an acceptable flavor, could be used as a high quality protein supplement for animal as well as human consumption, possibly providing another source of much needed protein supplement in underdeveloped countries.

For the preparation of the following Historical section the authors relied primarily on the 1889 review by Hermann Stillmark (6).

HISTORICAL

Castor beans have been found in Egypt in several ancient tombs estimated to be over 4,000 years old. The ancient Greeks and Romans were also familiar with castor bean plants. The Romans called the plant "cici" and the plant is also mentioned in the Bible (Jonas 4:6). The origin of the Latin word "ricinus" is not known. The word denotes both the castor bean plant (Ricinus communis) and the European tick (Ixodes ricinus). Because the bean resembles the tick, it is unclear whether the plant was named after the tick or vice versa. The Greek name "kroton" describes both the plant and the tick. The Romans called the plant the "louse tree" or "cici". However, the word "ricinus" may have originated from the Hebrew word "kikar" (round). In England castor seed oil was known as "kiki" oil. The Germans call the plant "Wunderbaum", the Dutch "Wonderboon" or "Christuspalm," and the French "Bois de Carapat" or "Paume Dieu". The Russian words for the plant and the tick also have a similar origin ("Kleshtschevina" vs. "Kleshtsch"). In India, the plant is described in the ancient Susruta Ayurveda (Medical Treatise), and the Sanscrit name for the plant is "Eranda" or "Revuka" (6). In Egypt the plant is called "Kharua", in Mexico "Higuerillo", in Cuba "Higuereta", in Venezuela "Tartago" and in China "Pi ma" or "Ta ma Tse" (7). Before WW I, France and other European countries imported castor oil from South and North America, including Canada. In that era Canada was known as "le pays des castors" (beaver country), hence the name castor oil (8).

Oil extraction from castor seeds was discussed by the Greek historian Herodotus ca. 400 B.C. as follows:

> the Egyptians obtain oil from the fruits of a shrub called kiki. They grow the plants from seeds, whereas the plant grows wild in Greece. They collect the seeds, roast them and then boil them. The oil that flows out is as good in the

> lamp as olive oil, but it smokes a great deal (6).

The Roman naturalist Pliny, ca. 50 A.D., was the first person to describe the properties and extraction procedures for castor oil: "the seeds are boiled and the oil that flows on the surface is poured off. The Egyptians obtain cleaner oil without using water or fire, by sprinkling clean seeds with salt and pressing the oil out." He also stated that the oil is too thick and does not give enough light (6). The Greek physician Dioscorea, ca. 50 A.D., states "the seeds should be dried in the sun until the shells fall off. Then they are pulverized in a mortar, boiled and the oil is poured off" (6).

Pliny's recommendation is to drink a mixture of warm water with an equal volume of oil to cleanse the body. He claims the drink will relieve aching feet and earaches, improve the color of the skin, renew growth of hair on bald spots, and enhance healing of skin burns (6). The ancient writers in the Middle East recommended castor oil for internal as well as external purposes. They recommended a mixture of 10 seeds ground with honey to be used for treatment of gout, swelling of joints, eye inflammation and skin disorders. A review of the medical uses of the castor bean plant has been published (7).

CASTOR SEED POISONING--CASE HISTORIES

In Stillmark's era (ca. 1880) there was a serious paucity of information on castor seed poisoning in humans. In his "Manual of Toxicology" published in Philadelphia in 1874, John T. Reese had described only one case of poisoning, and only one case had been mentioned in L. Lewin's "Lehrbuch der Toxikologie" published in 1885. Stillmark, therefore, reviewed and published a collection of case histories of castor seed poisonings in humans (6). References 9-30 and the corresponding cases are extracted from his publication. Some of the early references given by Stillmark are incomplete, and no effort was made by these reviewers to consult the original articles.

In 1738, two cases of castor seed poisoning were reported. A 24-year-old woman consumed about 0.2 g of castor seed for a laxative. Two hours later she became nauseated, weak, and frightened. After taking a theriaca and some milk, she was treated externally with a heart-stimulating plaster and clyster. The woman recovered (9).

A soldier consumed a similar amount of seeds. He developed severe diarrhea and was confined to bed for 20 days. After recovery he continued to suffer from stomachaches (9).

In 1818, Bergius reported a case of castor seed poisoning in a young man. The man chewed and swallowed one seed. The next day he developed diarrhea and vomited severely (10).

In 1823, E. Hale, a physician, was given an intravenous dose of 8 oz of his blood mixed with 0.5 oz of ricin oil. After 35 min he could taste the oil on his tongue, developed nausea, dizziness, stiffness of facial muscles, loss of speech, weakness, frequent bowel movements, and fever. He remained ill for 3 weeks and recovered (11).

In 1848, a young man consumed about 2 g of castor seed meal (seed residue from which the oil had been removed by pressure). He vomited continually for about 24h and almost lost his life (12).

In 1856, a person consumed an emulsion containing about 100 g of castor seeds. Vomiting and purging followed, and no other toxic symptoms appeared (13). In the same year a 54-year-old woman ate 5-6 castor seeds, and several hours later her pulse was weak; she developed edema of the lungs, contraction of facial muscles, diarrhea and chest pain. She was given large doses of ground up flax seeds and soda, and recovered in 3 days (14).

In 1861, a man died after eating 2-3 castor seeds. An autopsy revealed an inflammation of the stomach, and erosion and ulceration of the stomach and lining of the small intestine (15).

In 1862, a 2-year-old child drank some rancid ricin oil contaminated with castor bean particles. The child died of intestinal inflammation (16).

In the same year a man was hospitalized after eating 7 castor seeds. He suffered from vomiting, diarrhea, headaches, and muscle cramps in the back, legs and arms (17). Another report states that 2 patients drank about 30 g of castor oil and died within 3 hours. The oil may have been contaminated with seed protein (18).

In 1869, Pecolier reported 4 cases of castor seed poisoning. Two girls recovered after eating 5-6 seeds. They suffered from severe abdominal pains (19).

A 36-year-old woman ingested 3 seeds obtained from her neighbor's yard. Two hours later she felt weak, and vomited repeatedly (7-8 times). Later she had chest pains, headaches, hot skin, thirst, and weak pulse which persisted for 13 hours, in spite of administration of medications, including opium. The symptoms persisted for about 40 hours (19).

The fourth patient, a 20-year-old woman, ate 3 seeds but her symptoms of poisoning were not severe (19).

In another case (1869), a woman ate 5-6 g of ground castor seeds. Her symptoms included constant vomiting and bloody stools. She died on day 5. Postmortem findings included: inflammation of the stomach lining, accumulation of blood in the brain, liver, spleen and lungs, production of large quantities of bile in the gall bladder and coagulation of blood in the heart (20).

In 1870, a 6-year-old boy and a 3-year-old girl ate an unknown quantitity of seeds. The children recovered in 3 days (21). In the same year, an adult man ate 6 unripe castor seeds. Two hours later, he developed nausea, vomiting, and later diarrhea, cold sweat and collapse. He fully recovered in 3 days. The author claimed that the unripe seeds were more dangerous than the ripe seeds (22).

Another report stated that a physician prescribed the following laxative to his hospital patients: 1 tablespoon of a mixture consisting of 4-8 g ground castor seeds in 60 ml water. This tasteless and cheap medication, however, caused severe diarrhea in some patients. Other possible problems were not mentioned (23).

In 1871, a soldier ate 17 ripe, dry, 6-month-old castor seeds for an aperient effect. The seeds tasted like almonds. Three to 4h later violent diarrhea came on, followed by heartburn, nausea, and vomiting. He received 2 g of ipecacuanha. About 12h later his face was covered with cold perspiration, his eyes were upturned and he had frequent attacks of muscle cramps in legs. The pulse was very weak, but regular. He was treated with mallow clysters (enemas), mucilaginous lemon drinks, rhubarb, opium and meat broth. The urine after the first day was dark, albuminous and dense. For several days he felt weak, and developed a fever, but in 6-7 days he was fully recovered (24).

Other cases of castor seed poisoning were reported in 1871. A 6-year-old child ate 1-2 seeds which he mistook for beans. He developed severe abdominal pain, and was treated with sedatives and emetics. The child survived (25).

A man consumed castor seeds instead of castor oil and became severely ill. He complained of abdominal pains, and later developed convulsions and jaundice. One foot became gangrenous and had to be amputated. The outcome is unknown (25).

A woman suffering from migraine headaches ate an unknown amount of castor seeds. She became ill, developed severe diarrhea and died (25).

The Beadle Oil Co. in Boston discarded some damaged castor seeds. Several children playing in the street mistook the seeds for pistachio nuts and shared some with their friends. Seventy children became severely ill, but eventually recovered (25).

In 1875, an 18-year-old girl ate about 20 seeds, while her two younger sisters ate 4-5 seeds. The

oldest girl became ill 4-5h later, vomiting, with a stomachache and severe diarrhea. The following morning she had bloody stools, abdominal pains, and appeared to be confused. She collapsed on day 5 and died. Her stomach and intestinal lining was inflamed. The two younger girls recovered (26).

In 1879, a man ate about one-half of a castor seed, and in 5 min felt a burning sensation in the throat which extended throughout the gastrointestinal tract. A few minutes later he vomited and suffered from diarrhea. Steam inhalation, morphine, brandy and mustard plaster were administered as treatment. For the next 3 days he felt weak and suffered from abdominal pain (27).

In 1882, a child was given, as medication, 6-10 g of ground seeds and milk. In 5 days the child died. The autopsy revealed a normal stomach, but the entire small intestine was so inflamed that it fell apart when touched (28).

In 1888, 15 pre-school children (all under 6 years old) and their teacher each consumed 3 to 4 seeds, obtained from castor bean plants in the school yard. Vomiting and weakness lasted for 48h. No diarrhea was observed, and no medical treatments were related in the report (29).

Several cases of ricin poisoning were discussed in an 1888 Russian publication. A 26-year-old woman ate 6 or 7 seeds. After 2h she felt dizzy, weak, vomited, and had abdominal pains. Cold towels were applied over her chest and she was given black coffee to drink. Her pulse was 120 and her feet were very cold. She recovered fully in 5 days (30).

In another case, a woman poisoned with castor seeds began vomiting and complained of severe stomachaches. The stomach contents were washed out with warm water and she was given some amygdalin and opium. The patient recovered in 3 days (30).

A 49-year-old woman ate 12 to 15 castor seeds and in an hour felt weak, had shivers, vomited, felt a burning sensation in the throat and developed diarrhea.

Her reflexes were weak; her pulse (about 130) was barely detectable. She died in 3 days. Postmortem examination revealed numerous small bleeding areas in the stomach, the small intestines swollen, disintegrating and bleeding. No poison was detected in the intestinal contents, but a microscopic examination revealed swollen cells in the intestinal epithelium which contained pale and agglutinating red blood cells (23). The author stated that the poison in castor seeds acts primarily on the intestinal tract and recommended amygdalin as an antidote. After amygdalin formed cyanide in the organism, it would counteract the toxicity (30).

In 1900, a 26-year-old man ingested two seeds. That evening he complained of abdominal pains, followed by vomiting and purging. His extremities were cold, he perspired and his pulse was weak. The stools and vomited matter were watery, sanguineous and slimy. He died 6 days later. No treatment was described. An autopsy showed that the meninges, the brain, lungs and kidneys were congested, the heart was pale, and its cavities contained clots. The stomach was highly congested with scattered round erosions. There was an extreme congestion of the small intestine and great attenuation of the mucous coat (31).

In 1911, several cases of castor seed poisoning occurred in Australia (32). In a merchant's office a bag of seeds had broken open and the seeds had scattered on the floor. Five clerks chewed and swallowed some of them with the following results: (a) a male, 27 years old, chewed 6 beans at 4:00 p.m. on Thursday. He vomited at 6:00 p.m., and vomiting, purging and cramps lasted all night and all the next day. He was well enough to go his office on Saturday morning. All the symptoms recurred on Saturday afternoon. He collapsed with cold extremities, subnormal temperature, very weak pulse and had great difficulty in breathing. He remained ill for a week. (b) a male, about 29 years old, ate two seeds. He did not vomit, but the bowels were affected; he felt indisposed all next day. (c) a male, 22 years old, ate one seed, and it had no effect on him. (d) a male, 22 years old, ate about 6 seeds, vomited from 6:00 to 11:00 p.m., the bowels were very active, he had severe

headache, but went to work the next morning. (e) a male, 21 years old, ate about 8 seeds, he did not vomit, but had severe headache, and his bowels were very active, he was all right the following morning, (f) a male 15 years old, ate about 6 seeds, and vomited at 8:00 p.m. and continued vomiting until midnight. His bowels were severely affected, with resultant purging which did not cease until the next day. He remained in bed on Friday, and was well the following morning. Each of these five clerks suffered from a sore throat, the first symptom of poisoning. No treatment was discussed in this report (32).

In another case, the mother saw her 3 year old child eating one seed picked from a castor bean tree growing in her backyard. She shared the seed with her child; each ate half a seed. Both vomited all night, but were well the next day. The husband ate one with no ill effects. Her second child, 8 years old, ate 4 seeds. Five hours later she began to vomit. Her mother gave her castor oil, liquorice, barley water and soap enemas, and the child went to sleep. Next morning the child was found collapsed, unconscious, and she appeared dead. She was taken to the hospital where she remained in a collapsed condition for 4 days, with vomiting and purging. She was unconscious for 2 days, and was treated with the stomach pump and continuous saline injections. The child recovered, and her mother destroyed the castor bean trees (32).

The post surgeon at Cabana Barracks, Cuba observed a prisoner who ingested 14 seeds in the evening and became very sick after supper. He vomited all night, had pain over the region of his liver and cramps in his limbs. Two days later his temperature was 99°F, pulse was 70, and his respiration was 20. His blood was not examined, and his urine showed nothing abnormal. Treatment consisted of hot bottles applied to his sides, morphine administered hypodermically, a liquid diet, and bedrest. The patient recovered in 3 days (33).

Another prisoner ingested 6 seeds in the evening and became violently sick the next day. Nausea, vomiting and purging were the main symptoms. Headache, abdominal pain and cramps were also noted.

His temperature was 99°F, with a pulse rate of 70, and respiration of 20. His blood was not examined. His urine showed a specific gravity 1.033, with an increased amount of sulfate, and a trace of albumin. This patient also recovered rapidly under the same treatment as the first patient (33).

The third patient ate one seed after supper. His symptoms were identical to the 2 preceeding patients, but much more severe. His temperature was 95.3°F, the pulse rate was 102, and respiration was 24. His blood was not examined. Treatment consisted of injections and atropine to relieve the severe abdominal pains, and hot bottles were placed at his sides and feet. He was also given strychnine sulfate to stimulate the heart. The skin temperature was so low that 2 men had to rub his limbs to make him more comfortable. After several days he recovered (33).

The fourth man ate 4 beans in the afternoon and became violently sick that evening. He recovered 3 days later under the same treatment as the preceeding 3 patients (33).

These 4 patients were given castor seeds by a man who collected a large number of ripe seeds. After eating an undetermined number, he placed the remainder in his pocket and took them back to the barracks. The man said that he liked the seeds so much that he had eaten more than a handful of them without feeling any bad effects. The sergeant who was in charge of this detail also reported that he had eaten over 100 castor seeds and had suffered only slight cramps in the lower abdomen. These observations indicate a most marked difference in the individual susceptibility to the toxin in castor beans.

The author also describes a case of castor seed poisoning that occurred in 1902 in Baltimore. A young boy ate 10 to 12 seeds and shortly thereafter became violently ill. Two days later he saw a physician who treated him by administering cocaine, followed by morphine injections two days later. His condition did not improve, his mind became impaired, the skin became dry and cool, and was peculiarly mottled with varying color of pink to blue. His temperature was subnormal

but rose to 104°F when he died on the twelfth day. His blood seemed to be disintegrated (33).

A 1935 report describes clinical symptoms of castor seed poisoning. Two hours after a 24-year-old man ingested 15-20 castor seeds he felt nauseated. After spending the night vomiting, with abdominal pains and diarrhea, he entered the hospital the next morning. The patient was very ill; his face, hands, arms and legs were cyanotic; his skin and tongue were dry and the mucous membranes were a reddish color. His temperature was less than 37°C, his pulse rate was 110, weak and regular. He was unable to sleep and suffered from anuria and abdominal pain. Neither the liver nor spleen were enlarged. His heartbeat was weak and he had pain in the kidney region. The patient was given a laxative, an injection of ouabain, an infusion of 20 ml of hypertonic glucose solution, and a subcutaneous injection of caffeine and camphor. The patient was maintained on a liquid diet. Urinalysis of the patient, on the second day, showed an output of 50 ml of acidic urine, containing albumin and glucose, and a specific gravity of 1.015. Some erythrocytes and epithelial cells were present but no bile pigments, acetone, or ketone bodies. The fourth day he continued to have insomnia and his blood pressure was 170/100. His urine output had increased to 500 ml. By the sixth day his condition worsened. Diarrhea was present, his blood pressure had lowered to 150/100, and urine output increased to 700 ml. Strychnine was given subcutaneously. The following day his blood urea nitrogen was 4.64 g/l, but blood pressure was unchanged. At this time 200 ml of hypertonic glucose was infused. On the ninth day after consuming castor seeds, the patient had an increased output of urine to 2,500 ml, with a lowered specific gravity to 1.008. It now contained 0.4 g of albumin, some erythrocytes and leukocytes. His blood pressure continued to drop to 105/85. The following day his urinary output was further increased to 5,000 ml, with a specific gravity of 1.008. His blood pressure was 115/90, and he was given an oral dose of both Cardiazol and ephedrin. By the eleventh day his condition seemed slightly improved with a urine output of 2,000 ml. The urine had a specific gravity of 1.009, and contained 0.3 g of albumin. His blood pressure was 105/85 and the blood

urea nitrogen was 3.53 g/l. By the twelfth day his condition had worsened. He was developing acrocyanosis. His pulse was weak at a rate of 120. His blood pressure had dropped to 60/30, and he was hallucinating. Although he was again infused with hypertonic glucose containing Cardiazol and ouabain, his blood pressure continued to drop to 30/0, and he expired that evening (34).

It was concluded that the cause of death was nephritis, uremia, and disturbances in the peripheral blood circulation. The autopsy report of gross findings indicated that the deceased had a bleeding and congested stomach, a congested and enlarged liver, a soft, congested and enlarged spleen, no apparent changes in the heart with a soft myocardium and normal valves, slightly enlarged and congested kidneys with easily detachable capsules. The microscopic findings were congested gastric vessels, with hypertrophied follicles in the spleen, and occasional patches of pus formation. The intestines showed congestion along the entire length; hemosiderosis and necrotic areas dotted the liver tissues. There were enlarged pulp and pigments in the spleen, while the myocardium showed parenchymal degeneration. Anthracosis and pigment deposits in the lung were visible, while atrophy of glomeruli and areas of necrosis in the kidney confirmed the nephritis diagnosis (34).

It was concluded that the ricin poison affected the blood vessels and other cells causing slight hemorrhaging, necrosis, congestion, inflammation, and degeneration of liver, heart and spleen (34).

Castor seed poisoning is a common, typical childhood poisoning in Hungary (35,36). In those areas of Hungary where castor beans are grown for industrial use, occupational poisoning is also frequent (35). In one instance, 7 children were admitted to the hospital complaining of abdominal pain, drowsiness and vomiting. On day 5 they were discharged from the hospital. In another case, a 14-year-old boy was admitted on the third day after eating castor seeds. He was cyanotic and had a weak pulse of 132, irregular heart beat, frequent mucous stool and severe nephritis. His urine contained many red blood cells,

granular and hyaline cylinders and epithelial cells. The level of blood urea was 193 mg%. After appropriate dietary and therapeutic treatments, he was discharged on day 17. The level of blood urea returned to 14 mg% (35).

The following report describes castor seed poisoning in school children. An enterprising schoolboy who failed to sell castor seeds to a drugstore owner gave some seeds to his classmates, claiming that the seeds were "foreign nuts". Thirty minutes later the children complained of heartburn and abdominal pain; they became nauseated and vomited. Two hours later, 10 children ages 11-13 years were brought to the hospital. Each child was immediately treated as follows: gastric lavage, and injections of 0.5 ml "Pulsoton" (heart stimulant) and 0.4 ml 20% caffeine-sodium "benzoicum" to stimulate blood circulation. Five children were given a 10% Dextrose-Locke solution, including thiamin and ascorbic acid, to maintain their blood electrolytes. The lavage from some of the chidren contained small particles of castor beans. The number of ingested seeds varied from 1/2 to 6. After the treatment 6 children were sent home and 4 remained in the hospital for an additional 4 days. One child had protein in the urine and the level of urobilinogen in the urine was elevated in 7 children. After 48h these levels returned to normal. The hospitalized children complained of stomach and abdominal pain. On the second day 2 children had headaches, felt confused and weak. One child developed numerous petechiae on the chest and arms. The spots disappeared in 4 days. Electrocardiogram recordings were obtained daily for 3 days. In 5 cases the Q-T time was prolonged, one child showed a prolonged atrio-ventricular conduction time (0.21 sec), and one had a minimal repolarization of the right chamber. These changes were absent 4-5 days after the poisoning. Clinically, the gastrointestinal symptoms predominated, but the patients also suffered with headaches, dizziness and depression. The urobilinogen levels in the urine indicated there were some problems in liver function. The levels of serum electrolytes did not change despite frequent vomiting. It is emphasized that the castor seed poisoned patient should be treated with gastric lavage, cardiac and

circulatory stimulants, and electrolyte replacement therapy as soon as possible (37).

In 1955, 120 cases of castor seed poisoning were treated in a Russian medical facility (38). Neither the location of the hospital nor the region where the poisoning occurred is provided. The article states that the patients sought initial help at the local medical facilities, which in turn alerted the population in their district. The patients reached the hospital 2-3h after ingesting castor seeds. The patients included 5 children 4-10 years of age, one 15-year-old, and the remaining ranged from 20-25 years. Eighty-nine patients were hospitalized from 4 to 7 days, 24 patients from 8 to 14 days and 7 patients from 15 to 29 days. The first symptoms of poisoning appeared 1-2h after ingesting the seeds; 99 patients felt nauseated and 92 vomited repeatedly; 73 complained of abdominal pain; 53 had severe diarrhea. Three patients were suffering from chronic dysentery which was exacerbated by castor seed poisoning (38).

One patient ingested about 200 seeds. He had severe abdomial pain, swelling in the upper part of the abdomen, and strong peristaltic movements of the bowels (38).

About one third of the patients felt some weakness, complained of headaches, dizziness and thirst. Four to 5h after poisoning, 29 patients had facial hyperemia, 7 had hyperemia of the mouth, 2 had cyanotic lips, and 33 complained of tenderness of the abdominal region during an examination. Breathing was not affected (38).

In 13% of the patients a decrease in pulse was observed, and in 27% an increase was noted. No changes in the circulatory system were observed the day after poisoning. Liver palpation did not cause pain. Urobilin test was negative in 79 patients, weakly positive in 15, and positive in 6 patients. When the urine specific gravity from each of 92 patients was measured, 19 were below 1.015 and the remaining were above 1.015 (38).

Blood urea nitrogen level was determined in 51 patients; in 3 patients the level was above 50 mg%, in another 3 it was between 40-50 mg%, in the remaining 45 it was below 40 mg%. Urine from 4 patients was examined for protein. In 3 patients the urine contained erythrocytes (38).

The effects of castor seed poisoning on liver and kidney function are illustrated in one severely ill patient: A 20-year-old man was brought to the hospital complaining of weakness, dizziness, and headache. He vomited frequently, including some blood, and had abdominal pains. He had ingested about 60 seeds. His temperature was normal; his blood pressure 120/80; and his pulse rate was 80. The upper part of his abdomen was painful when palpated. Blood urea nitrogen increased to 75 mg%. Before he recovered, his leukocyte count rose to 24,000 and his serum bilirubin was 3 mg%. The patient was hospitalized for 24 days (38).

After arrival at the hospital, many patients continued to vomit. They were treated with a gastric lavage which reduced the frequency of vomiting. Then they were administered oil of camphor and caffeine. They were also given magnesium sulfate (25 g) and treated with clysters. Serious cases were given glucose or saline, intravenously or subcutaneously. Other interventions were provided as indicated by the symptoms (38).

After observing these poisoned patients, the Russian investigators used guinea pigs to study the toxicity of castor seeds. Six animals were given ground seeds mixed with 25 g of oats as follows: 2 animals were given 1 seed each, 2 animals were given 2 seeds each and 2 animals were given 3 seeds each. The controls were given oats only. The experimental animals consumed about 1/5 of the amount of food eaten by the controls on the first day, and stopped eating the following 2 days. One to 2h after eating, the seed-fed animals became listless, and did not respond to human touch. By the second day the fecal material contained blood. One animal from the group eating 2 seeds died on the second day. It was calculated that

this animal consumed about 0.16 g castor seeds. The other experimental animals recovered (38).

In another experiment, 3 guinea pigs were each fed a diet consisting of millet, milk, bread, oats, and 3 ground castor seeds/25 g of food. Animals were killed on day 1, 2 and 4. Autopsies showed that the gastrointestinal tract of these animals contained areas with massive hemorrhage, emphysema and edema in the lungs and edema in the brain. Histologic findings revealed vascular changes in the stomachs and along the entire intestinal tracts, as well as necrotic areas in the large intestines. Cells of intramural ganglia exhibited dystrophic changes. Some changes were observed in lipid and protein components of hepatic cells, swelling around the capillaries, hypertrophy of reticular cells, and venous congestion. The spleens were congested, with a moderate follicular hyperplasia. The kidneys showed pronounced dystrophy with severely congested glomeruli. Tissue dystrophy and congestion in the hearts were also found. Along with edema, congestion and emphysema in the lungs, the experimental animals displayed swelling and congestion in the brain. These morphologic findings were then compared with those in a patient poisoned with castor seeds (38).

The patient, 23 years old, was hospitalized, complaining of abdominal pain, dizziness and vomiting. He had ingested about 100 castor seeds. The next day he developed acute chronic dysentery. Blood analysis showed nothing abnormal, the level of bilirubin was within normal limits. Some urobilin was detected in the urine. The patient was hospitalized for 3 weeks. After his condition improved and he was to be released, he suddenly died of an accidental head injury. An autopsy revealed some hypertrophy in the large intestine and swelling in the underlying tissues, dystrophy of hepatic cells, and pronounced infiltration in the periportal tissues. There was intense swelling in the kidneys, and sclerosis in the glomeruli together with lymphoidal infiltrations. Some congestion and edema were found in the lungs. There was heavy swelling of muscle fibers in the heart. These findings are consistent with castor seed poisoning (38).

A report from Argentina briefly describes castor seed poisoning in a child. A boy of 7 years ingested 8 seeds. (A lethal dose for a child is 3 seeds). Ten hr later, symptoms of severe poisoning appeared, although some seeds were not chewed, and they passed through his body intact. Clinical symptoms included severe vomiting and diarrhea with traces of blood, severe abdominal pain and general weakness. The abdomen was sensitive to palpation. He had no fever. There was an increased pulse rate with normal intensity. The profile of blood electrolytes was normal. He received no medication and was well on the following day (39).

Eight cases of human poisoning occurred in the dock workers at the Stetin harbor when they consumed spilled castor seeds they mistook for edible nuts. Toxic symptoms appeared between one-half and 4h after they ingested 1-1/2, 2, 3, 5, or 10 seeds. Two out of 3 ambulatory cases developed gastrointestinal problems, and 1 patient showed acute allergic problems, including laryngeal edema, bronchial asthma and conjunctivitis. Five people were hospitalized due to nausea, severe vomiting, diarrhea and abdominal pains. Two patients complained of headaches. Overall symptoms of poisoning were fairly light in 4 patients, 1 patient developed circulatory problems, 4 patients developed bradycardia, and according to their EKGs, 3 patients showed changes in repolarization, apparently as a result of changes in the level of blood electrolytes. No changes in the activities of serum transaminases were observed, and only in one case were there some red blood cells in the urine. No hemorrhagic complications or damage to internal organs were observed. The treatment consisted of an early gastric lavage, and the administration of papaverine hydrochloride, atropine and carbonate (40).

In another case, a 43 year-old dock worker began complaining of abdominal pains, nausea, vomiting and diarrhea shortly after completing his breakfast (bread and dry salami). These symptoms lasted for 2 days. A physician prescribed a laxative and sulfaguanidine. Since the patient felt weak, he was admitted to the clinic. At that time his wife explained that he had ingested "some nuts similar to beans". The patient was in a serious condition, with dry, grey and cold skin, the lower extremities had a mottled appearance, and his

respiration rate was increased. The pulse was weak, with a rate of 120/min. The upper abdominal area and chest were painful for the patient when touched by the physician. The patient was unable to urinate. The concentration of urea and potassium in the serum was 245.52 mg% and 3.9 mEq/l, respectively (41).

The patient was infused with noradrenaline, 30-40 mg in 200 ml of 5% glucose solution. The total amount of the administered noradrenaline was 480 mg, 3 ampules of "hipertensyn" and 375 mg of hydrocortisone. The patient died about 15h later. An autopsy revealed mild edema of the meninges and the brain, edema of the lungs, fluid in the intestines, degenerative changes in the liver and renal cortex. An histologic examination showed a severe degeneration of kidney tubules (41).

In another report from Poland, a 42-year-old man ingested 10 seeds and about 5h later developed symptoms of food poisoning. His condition worsened every hour and he was sent to the hospital. The patient stated that he was transferring some seeds at the railroad station, and mistook them for peanuts. Two others in his group also ate several seeds but they developed only mild gastrointestinal problems and did not require medical help. Upon arrival at the hospital the patient looked pale, was covered with cold sweat, his eyes were sensitive to light, and he had a dry mouth. He had pain in the abdominal region and the chest. The third day his condition worsened, and vomiting became more frequent. A further worsening of his condition was noted on day 5, when his abdominal pain increased, accompanied by the onset of arrhythmia, a weak heart beat, and a pulse of 140/min. The electrocardiogram showed damage and anoxia of the cardiac muscle. This condition persisted for an additional 5 days. However, on day 11 his condition had improved. The abdominal pain and vomiting had subsided, the heart rate had dropped to 80 beats/min., the pulse was regular, and the blood pressure was 110/75 mm Hg, blood leukocyte count was 6,900 and the urine was normal. A marked improvement in the heart condition was observed. Several days later his red blood cell count was 5.14 million, and the white blood cell count was 9,800. He had traces of protein in the urine, but no sugar. His continuing treatment included cardioactive drugs, such

as "strophanthin", "phenactyl", "detreomycyne", and a transfusion of 250 ml of blood. The patient was released from the hospital on day 21 (42).

A report from Holland describes a case of poisoning caused by chewing a single castor bean. A 57-year-old man found some castor seeds on the loading docks at Amsterdam harbor. Since the seeds appeared to him to be similar to those grown in his garden (pronkbonen), he chewed and swallowed one seed. Shortly thereafter he felt a burning sensation in his mouth, throat and lips. The next morning he described the beans to his friend who later found him unconscious in the bathroom. He was taken to an emergency room and the medical personnel were informed that the patient had ingested a castor seed. The patient was treated with 1 mg of adrenaline subcutaneously and with 25 mg prednisolone intravenously. His pulse rate was 100/min, temperature 36.8°C, blood potassium 3.0 mEq/l, and serum GOT 82 units. His electrocardiogram and X-rays were normal. The patient was given 500 ml of physiological saline intravenously and 1 mg of adrenaline subcutaneously. This was followed later with an infusion of 500 ml of dextran, and 1 ampule of Calcium-Sandoz, administered intramuscularly. By midday his blood pressure was 130/85, and he was given 500 ml of saline containing 1.5 g KCl. That afternoon the patient felt well and asked to be released from the hospital. The following night he developed severe diarrhea and remained hospitalized another 4 days (43).

The Dutch physician who related this case stated that there is no known antidote for castor seed poisoning, and the treatment is strictly symptomatic. The following treatments were proposed: (1) gastric lavage, (2) injections of 50 mg papaverine-HCl, (3) restoration of the electrolyte balance, (4) prevention of precipitation of hemoglobin in the renal tubules by making the urine alkali... with injections of 1.3% sodium bicarbonate. Later the bicarbonate solution can be administered orally. Patients in shock should be given an infusate of Dextran-40, a plasma extender, containing 5 to 10 mg of adrenalin per 300 ml. Metaraminol can be t- substituted for noradrenaline. In addition, a schedule of injections of 25 mg/ml of a prednisolone solution should be started with 6

injections the first day, 4 injections the second day, and 2 injections the third day. An unspecified aliquot of injections of a 10% solution of calcium gluconolactobionate for shock treatment is recommended. Finally, if cramps develop, 100-500 mg of phenobarbital may be given, or if the cramps are severe, Penthothal may be administered (43).

In the course of one year, 4 cases of castor seed poisoning were reported in India. The patients were male, 7 to 18 years of age, who inadvertently swallowed 1 or 2 seeds. In the hospital their blood samples were analyzed for urea, cholesterol, sodium, potassium, and chloride. Blood levels of bilirubin and alkaline phosphatase were determined to test for liver function. The results showed that poisoning with castor seeds was capable of elevating the blood urea level up to 272 mg% where it could remain for more than a week. All the other tests were in the normal range (44).

The same authors studied castor seed toxicity in rats. An extract was prepared by vigorously shaking 10 mg of powdered castor seeds with 3 ml of saline. After centrifugation, 2 ml of the supernatant fluid was used for gastric intubation. The rats were given the saline extract every day for 4 days. The data showed that the kidneys were most greatly affected. The spleen also showed congestion. Renal alkaline phosphatase activity was normal. There was a four-fold increase in blood urea levels (44).

In 1977, 4 family members in Italy were admitted to the hospital after ingesting castor seeds. The father was 44 years of age, the mother 41 years, the son 12 years, and the daughter 8 years. The severity of the poisoning symptoms was related to the number of the seeds that had been eaten (45).

The son ingested 2 seeds. He experienced myosis the first day, complained of nausea and vomiting for 3 days, had no diarrhea, and was the first to completely recover. Levels of blood urea were increased and traces of protein were found in the urine. The patient was treated with sodium carbonate (500 ml), Trinidex (1,000 ml), Laevoson, 5% (500 ml), and on day 4 with 5% glucose (1,000 ml). He was released on day 9 (45).

The father ingested 3 seeds. The first day he experienced myosis, nausea and vomiting. These symptoms stopped the third day. Blood urea was elevated to 280 mg%, and there was protein in the urine. He was given the same treatment as his son, and was released on day 10 (45).

The mother ingested 8 seeds. She also experienced myosis the first day, followed by vomiting and copious bloody diarrhea for 5 days. She was treated with solutions of sodium carbonate (500 ml), sodium and ammonium chloride, sodium sulfate (1,000 ml), and 5% glucose (500 ml) each day for 7 days. Blood urea was elevated to 380 mg%. She was released on day 12 (45).

The daughter ingested about 10 seeds. The first day she experienced drowsiness, nausea, vomiting, violent abdominal pains and copious diarrhea. The third day vomiting ceased and diarrhea stopped the following day. Blood urea levels reached about 240 mg%, the urine contained protein, hyalin casts and some erythrocytes. She was given sodium carbonate (500 ml), 5% glucose (500 ml), and isotonic saline (500 ml) for the first 2 days; then vitamin K and cocarboxylase was included during the following 5 days. The ninth day she received vitamin B and C, and was released on day 12 (45).

A warning about castor bean poisoning in the United States appeared in a 1981 publication. Two girls, ages 4 and 5, living in a small southern Indiana town, found a canister containing walnuts and castor seeds. Each child chewed about 4 seeds. Ten hours after the ingestion, the 4-year-old girl began complaining of severe abdominal pain associated with numerous emeses, marked lethargy and multiple loose stools. She was taken to the local hospital where she received gastric lavage, dicyclomine hydrochloride and intravenous fluids. She complained of severe, colicky abdominal pain. Laboratory results included 1+ hematuria in her initial urine analysis and elevated serum hemoglobin (21 mg/dl). She was continued on intravenous fluids for 24h (46).

Her 5-year-old cousin began episodic vomiting with severe colicky abdominal pain 12h after castor seed ingestion. She received treatment similar to that administered to her cousin. She complained of severe abdominal pain and nausea. After intravenous fluids were continued overnight, the laboratory tests indicated normal values (46).

Three cases of castor bean poisoning, all in the course of 1 week, occurred in the St. Louis area. A 6-year-old boy ingested one-half of a seed. The Poison Center advised inducing emesis with syrup of ipecac and the child was brought to the emergency room. Laboratory tests included complete blood count, urinanalysis, liver enzyme determinations, and blood urea nitrogen. The patient was started on mildly alkalinized parenteral fluids. After 48 hours the treatment was stopped and the child was discharged on the third day (47).

A 4-year-old boy ingested portions or all of four castor seeds which had been used to make an ornamental necklace. Emesis was initiated at home with syrup of ipecac, followed by charcoal and cathartics in the emergency room. The evaluation and treatment for the child was the same as the above 6-year-old patient. The boy was discharged on the third day (47).

A 2-year-old girl ingested at least one castor seed. The child was given syrup of ipecac in the hospital and placed on outpatient status. Complete urine analysis was followed for three consecutive days, and all values remained within normal limits (47).

Possible teratogenic effects of castor seeds are discussed in the report of a 20-year-old woman who ingested one seed each month for 5 consecutive months, an old custom in Libya to prevent pregnancy. When advised by an obstetrician that her urine test for pregnancy was positive, she immediately discontinued castor bean ingestion. No other drugs were given during pregnancy. The neonatal period was normal, but from her 40th day of postnatal life, the baby developed spontaneous frequent convulsions and high fever. When the baby was admitted to the hospital, an examination revealed moderate growth retardation, cranio-facial

dysmorphia, and the fingers on both hands were thin and pointed. The terminal phalanges and fingernails of the fourth and fifth fingers were absent. The fifth toe was missing from each foot (48).

Castor seeds were used in a suicide attempt. A 21-year-old botany student, attempting suicide, ingested 30 seeds. Some of the seeds were chewed. Three hours later he developed a severe diarrhea, vomiting and abdominal pains. He was admitted to the hospital, and on the seventeenth hour he began shivering without fever, complained of acute abdominal pain, had nausea, diarrhea, cramps in the limbs and blurred vision. He was severely dehydrated, had lost five kg in body weight, and developed cyanosis of the extremities. His blood pressure was 100/80 and the pulse rate 106/min. There was an increase in blood urea nitrogen to 72 mg%, but serum creatinine, glucose, sodium, chloride, and potassium were normal. Increases in hematocrit to 57%, hemoglobin to 19 g/dl, and red cells to 5.5 million were noted. Liver function tests were normal and there was no evidence of hemolysis. Treatment was symptomatic, consisting of parenteral fluid infusions over four days. Every day the patient received one liter of saline, 3 liters of 5% glucose and 9 g of potassium chloride. He recovered rapidly, and on the third day he regained the body weight. He was dismissed on the fifth day (49).

In Israel, 6 children were hospitalized after eating castor seeds while playing in the garden of their home. (a) A girl, 12 years old, was admitted 5 hours after ingesting 5 seeds. The girl was pale and vomiting, with a pulse rate of 96/min, her blood pressure was 110/70 and her body temperature was 38°C. She complained of severe pains in the lower abdomen. Her hemoglobin was 16.2 g/dl, white blood cell count 14,500, blood urea nitrogen 36 mg/dl, and creatinine 1.0 mg/dl. The activities of serum glutamic-oxaloacetic and glutamic-pyruvic transaminase were increased to 35 and 32 units, respectively, and the activity of alkaline phosphatase was 662 units. The serum level of bilirubin was 3 g/dl. Her urine contained glucose (1.3 g/dl) and some albumin as well as red and white blood cells (50). Upon arrival at the hospital, the girl was treated with gastric lavage,

activated charcoal, and infusion of liquids containing bicarbonate. She continued to complain of headaches, abdominal pains, and vomited repeatedly. She had severe diarrhea and bloody stools. Her blood pressure dropped to 70/40, and her pulse rate was 108/min. Ventricular extrasystolic beats were detected. After 6 days her diarrhea stopped and her condition improved. Blood urea nitrogen dropped to 8 mg/dl, and liver enzyme values returned to normal. She was released from the hospital on day 9 (50).

(b) A girl, 4 years old, was admitted to the hospital about 3h after ingestion of two seeds. She complained of intense abdominal pain, nausea and vomiting. Her heart rate was 100/min, her blood pressure 80/60 and body temperature 38°C. Her electrocardiogram was normal. Laboratory tests showed: hemoglobin 13.5 g/dl, white blood cell count 11,600, blood urea nitrogen 20 mg/dl, increased activity of serum glutamic and pyruvic transaminase to 47 and 35 units, alkaline phosphatase 580 units. Slight metabolic acidosis and some albumin in the urine were detected. Upon arrival at the hospital, the girl was treated with gastric lavage and infusion of liquids containing bicarbonate. The next day her condition worsened; abdominal pains, vomiting and diarrhea became more intense. The electrocardiogram showed a few extrasystolic beats. Over the next 3 days her condition improved and she was released from the hospital on day 6 (50).

(c) A girl, 12 years old, was admitted to the hospital about 5h after ingestion of 5 seeds. Her heart rate was 100/min, her blood pressure was 90/60 and body temperature 37.8°C. She complained of severe abdominal pains, nausea and vomiting. Her white blood cell count was 9,700, hemoglobin 16.5 g/dl, alkaline phosphatase 607 units, serum GOT and GPT 36 and 37 units, repectively, and blood urea nitrogen 25 mg/dl. The girl was treated with gastric lavage, activated charcoal and infusion of liquids with bicarbonate. Her condition improved on the third day, and she was released the next day (50).

(d) A girl, 12 years old, was hospitalized about 20h after ingesting 3 seeds. She complained of nausea,

vomiting, headache and abdominal pains. Her heart rate was 100/min, her blood pressure was 110/80 and temperature 37.8°C. Her blood count and liver and kidney functions were normal. She was treated with gastric lavage, infusion of liquids and activated charcoal. The girl was released from the hospital on day 4 (50).

(e) A boy, 8 years old, was hospitalized about 3h after ingestion of 2 seeds. At admission he looked pale and continued vomiting. His heart beat was 96/min, his blood pressure 90/60 and body temperature 37.5°C. His blood urea nitrogen level was 27 mg/dl, and serum GOT and GPT 37 and 35 units, respectively. After admission he was treated with gastric lavage, activated charcoal and infusion of liquids. Five days later his condition improved and he was released (50).

(f) A boy, 6 years old, was hospitalized about 10h after ingesting an unknown quantity of seeds. He had severe abdominal pains, watery diarrhea and vomited frequently. His heart rate was 90/min and regular his blood pressure was 90/55 and body temperature 37.8°C. Laboratory tests showed normal liver function and his blood urea nitrogen was 20 mg/dl. He was treated with gastric lavage, activated charcoal and infusion of liquids which lasted for 2 days. His condition improved and he was released from the hospital on day 5 (50).

An accidental castor seed poisoning occurred in Great Britain. An 11-year-old schoolboy removed the outer husk of one castor seed before chewing and swallowing it. Castor seeds, along with 4 other different seeds were used in a classroom project. The boy was treated with gastric lavage, and remained hospitalized for 4 days. During this time he was given magnesium sulfate and activated charcoal. Apart from some initial generalized tenderness in the epigastrium, he remained well (51).

In the United States, a 21-year-old man ingested about 12 seeds that he had mistaken for hazelnuts. He experienced no burning in the throat. Approximately half an hour later he began vomiting profusely, 15-20 times. He continued to feel nauseated and 2h later he

saw a physician. He was given 2 doses of syrup of ipecac, followed with activated charcoal and magnesium citrate. About 8h after ingesting the castor seeds he was admitted to the hospital. The patient was nauseated, with a pulse of 100/min, his respiration was 20/min, and blood pressure was 130/70. Abdominal examination revealed a scaphoid abdomen with a hypoactive bowel sound and no tenderness. Initial blood urea nitrogen was 16 mg%, and creatinine 1.1 mg%. Serum sodium, potassium and chloride levels were within normal limits. Prothrombin time was normal, glucose 159 mg%, leukocytes 14,200, hemoglobin 15.6 g, and the hematocrit was 45%. Liver function tests were normal. A solution of D5 in 0.5 normal saline containing 20 mEq/l KCl was given at the rate of 200 ml/hr for the first 12h. He was also given a solution of calcium carbonate and ascorbic acid. His diarrhea abated after about 12h. On the third hospital day, his serum creatinine rose to 1.5 mg%. All other laboratory values remained within normal limits, and he was asymptomatic. He was discharged on day 4, although his creatinine level remained high at 1.4 mg%. The level returned to normal 2 weeks later (52).

An 80-year-old woman was found chewing seeds that had previously been shelled and prepared for planting. When admitted to the hospital, she had a 2h history of vomiting, diarrhea and abdominal cramps. Her blood pressure was 140/90, pulse 100 beats/min, respiration 20-24/min, and temperature 37.1°C. Her abdomen was diffusely tender, especially in the epigastrium. At the time of admission, laboratory test values were leukocytes, 7,800; hemoglobin, 13.9 g/dl; hematocrit, 41%; glucose, 103 mg/dl, and blood urea nitrogen, 25 mg/dl. Electrolytes were within normal limits. Initially, 60 g of activated charcoal in 70% sorbitol solution was administered. This was followed by 50 g in solution every 3 to 4 hours. The patient experienced periodic vomiting of the charcoal solution, and had a large amount of diarrheal stools throughout the day. Intravenous fluids were continued. Abdominal pain and diarrhea continued throughout the second day. The blood urea nitrogen value increased to 37 mg%, and creatinine increased to 2 mg%. The infusion rate of intravenous fluids was increased, and activated charcoal in sorbitol solution was discontinued. On the

third day after admission, the patient's gastrointestinal symptoms had resolved. She became increasingly pale and lethargic, and her extremities appeared somewhat cyanotic. Her blood urea nitrogen was 43 mg/dl, hemoglobin 17.6 g/dl, and hematocrit was 54.1%. A diagnosis of dehydration, secondary to hypovolemia was made. Intravenous fluid therapy was evaluated and fluids were increased to correct the fluid deficit. The patient's condition had improved by the fourth day. No diarrhea or gastrointestinal distress was observed for over 24 hours. The following day the patient's condition continued to improve, her vital signs had stabilized and blood urea nitrogen fell to 24 mg/dl. Later, she was discharged (52).

In Spain, a 45-year-old woman ingested 10-15 castor seeds. About 45 minutes later she complained of abdominal pain and profuse diarrhea. Upon arrival at the hospital she was treated with an infusion of physiological fluids and glucose. A solution of sodium bicarbonate was administered to increase the pH of the urine. In addition, 50 gm of activated charcoal was given orally. The laboratory values, as well as the liver function test, were within normal limits. She was discharged on day 6 (53).

DISCUSSION

The impetus to write this review arose after reading a thesis entitled "Ueber Ricin, ein giftiges Ferment aus den Samen von Ricinus Comm. L. und einigen anderen Euphorbiaceen." The thesis was submitted in February 1888, by Hermann Stillmark to the Medical Faculty der Kaiserlichen Universitaet zu Dorpat, Estonia, in partial fulfillment of the requirement for his medical degree. The work was expanded and published in 1889 as "II. Ueber Ricin" von Hermann Stillmark, in the "Arbeiten des pharmakologischen Instituts zu Dorpat" (6). Hermann Stillmark was born 22 July 1860 in Pensa, Estonia. He attended the "Ritter- und Domschule" in Reval (Tallinn) and later studied medicine in Dorpat. After graduation from the University, he was in private practice in Merjama and later, in Helmet. From 1895, he was a factory, railway, school and prison physician in Pernau (Estonia). It was, indeed, both instructive and

enjoyable to read his work and follow his many attempts to isolate the toxic principle from castor seeds, as well as his description and interpretation of the toxic effects observed in experimental animals. In his publication, he took the liberty to discuss problems not directly associated with his scientific endeavors, such as his concern over the potential danger of castor bean meal left in open fields in the Russian countryside, and about a manuscript that was lost on its way from Sydney to Dorpat. The fresh seeds used in his experiments were purchased in Erfurt, Germany and castor bean meal was ordered from Moscow. He found it disturbing that he was not able to obtain any information from Erfurt on the origin of the seeds, nor the oil extraction process used in Moscow. Stillmark gave the name "ricin" to the toxic compound in castor seeds. He was also the the first person to publish the observation that ricin agglutinated erythrocytes. This information immediately attracted the attention of Paul Ehrlich who, in the 1890s, established some of the fundamental principles of immunology (54,55).

This report presents a history of castor beans and an overview of poisoning which occurred in humans as a result of castor bean ingestion between 1738 and 1988. A lack of understanding of the toxic nature of castor seeds or the inability to correctly identify the seeds accounts for a significant portion of observed injuries. In several instances, however, the recognized toxic nature of castor seeds was exploited by professional assassins, or by others bent on destroying human lives. One to 3 seeds may be fatal to a child, 2 to 4 seeds may be poisonous to an adult, and 8 may be fatal to an adult. Fortunately, the seeds must be well chewed before ricin is released. If the seeds are swallowed whole, systemic toxicity is unlikely to appear because the seed shell is quite hard, which tends to prevent release of the ricin. Thus, the quantity of ricin available for absorption depends on the degree of mastication. Ricin resists the action of proteolytic enzymes in the intestinal tract, and presumably, is absorbed without being hydrolyzed. Thus, it is difficult to estimate the lethal oral dose of ricin for man. The values reported in the literature are: 30 mg (34, 37, 40), 0.03 mg/kg (43), or 1 mg/kg (49). The ricin concentration in a

single castor seed is about 3% (43, 44). Eight seeds, weighing about 0.6 g each, would contain 144 mg of ricin, or a dose of 2 mg/kg for a 70 kg man, assuming absorption is complete before its exit from the intestine. A portion of the ingested seeds would be very likely removed from the gastrointestinal tract by vomiting and diarrhea; the true lethal dose would be somewhat lower than the above figure. For comparison, the lethal dose of castor seeds (g/kg body weight) reported for domestic animals is as follows: hen, 14.00; goat, 5.50; duck, 4.0; pig, 2.30; cow, 2.00; sheep, 1.25; rabbit, 0.90; calf 0.50; goose, 0.40; horse 0.10 (56).

Successful early treatment is contingent upon a knowledge of consumption of castor seeds and the symptoms and signs of poisoning which may appear after a latent period of several hours, even several days. There are confirmatory immunoassay tests available in cases where ricin poisoning is suspected (57-59). The medical facility, however, may not be able to conduct such a test on short notice, and the assays are complicated by the fact that a portion of the ingested ricin binds to red blood cells and to serum proteins. A need for a simple and reliable test is apparent. The manifestations of poisoning often start with a burning sensation of the mouth and throat, followed with weakness, nausea and headache, severe abdominal pain, drowsiness, disorientation, cyanosis, mottled appearance of the skin on the extremities, stupor, convulsions, violent vomiting and profuse diarrhea. The vomitus and stools may contain blood. The resulting dehydration may cause cardiovascular collapse or acute kidney failure, and may lead to tachycardia, oliguria, hypotension, and even shock. Data obtained from terminal cancer patients injected with ricin show that about 75% of the dose remains in blood after 1 hour, and about 7% after 24 hours (57).

The plasma levels of ricin in one man who survived castor bean poisoning ranged from 1.5 ug/l on day 1 and 2, to 1.0 and 0.9 ug/l on day 3 and 4 (49). Thus, it is obvious that once absorbed, the circulating ricin can affect any organ or tissue. The kidneys, liver, and the intestinal tract are particularly prone to ricin injury. More severe poisoning brings about

disturbances in the central nervous system, including paralysis of the respiratory center. Hemorrhage throughout the heart muscle, pancreas, adrenals, testicles, and lymph glands is a common feature of ricin poisoning. Other manifestations include lung and brain edema, conjunctivitis, optic nerve lesions and mydriasis. The urine may show protein, casts, red blood cells and epithelial cells, and hemoglobin. The blood may show an increase in urea and non-protein nitrogen. Victims who survive may be quite ill for 3 to 14 days. From this brief and very incomplete list of metabolic and physiologic derangements observed in humans poisoned with castor seeds, it is difficult to answer the question, "Why does ricin kill?" Ample evidence shows that ricin inactivates the 60S ribosomal subunits, causing disruption in protein synthesis and cell death (60). Then, another question arises, "Why does the organism die, since protein synthesis in various organs is only partially inhibited?" Perhaps ricin affects some specific proteins, which are involved in a process of vital importance to the cell, thereby giving rise to some of the pathological consequences described above. One possibility, among many others, is that ricin has a selective effect on blood vessels causing severe interstitial hemorrhages. We do not really know why ricin kills, and as a consequence, there is no specific treatment for castor bean poisoning. Treatment is entirely symptomatic.

Recent experimental data show that radiolabeled ricin is rapidly distributed throughout the body after an intravenous administration to rats. The liver contained 46% of the injected dose at 0.5 hr. The spleen and muscle contained 9.9% and 13% of the dose, respectively, at 0.5 hr. However, the greatest concentration of radioactivity was in the spleen (33% of injected dose/g) compared with the liver (7.4%/g) and the bone marrow (5.5%/g). More than 70% of injected radioactivity was recovered in the urine as low molecular weight, freely diffusible metabolites (61).

From the reviewed cases of acute castor seed poisoning, it is apparent that ingested seeds must be promptly removed either by gastric lavage or emesis, using syrup of ipecac and/or activated charcoal to

absorb the ricin. The patient's fluid balance and serum electrolyte status should be closely monitored to prevent dehydration and ensuing complications. The urine should be made alkaline by giving daily sodium bicarbonate to prevent precipitation of hemoglobin in the kidneys. The liver and kidney functions, and hematology should be carefully monitored. Parenteral nutrition may be required if vomiting and diarrhea persist, and convulsions should be controlled by appropriate drugs.

CONCLUSIONS AND RECOMMENDATIONS

* The high toxicity of castor seeds has long been recognized. It is due to ricin, a small molecular weight protein, consisting of two peptide chains linked together by a disulfide bond. The seeds must be chewed before the toxin is released. One to 2 seeds may be fatal for a child, and 3 to 8 for an adult.

* Toxic symptoms may be delayed for as long as 24 hours after a person has ingested castor seeds.

* The mechanism of toxicity of ricin is inconclusive. Consequently, there is no known antidote for castor seed poisoning.

* Currently, treatment is symptomatic and supportive, with particular emphasis on replacement fluid and electrolyte balance after induced emesis and/or charcoal absorption of toxin.

* New insights into the molecular and histopathologic basis of castor seed induced injury will offer a new and rational approach to medical intervention.

* Detailed studies of castor seed toxicity should be conducted with laboratory animals. A known quantity of decorticated, defatted and pulverized beans could be incorporated into the diet or administered, in a suspension, by a stomach tube.

* The proposed experimental model could be used to study the mechanism of toxicity, and in larger animals (pigs) the course of clinical symptoms of toxicity.

* Such studies should include methods of detection and identification of ricin in tissues and body fluids, and development of protective and therapeutic measures. Early diagnosis would allow an appropriate medical intervention during the latent period before the appearance of toxic symptoms.

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